Systemic sclerosis: A world wide global analysis

Article *in* Clinical Rheumatology · April 2009

DOI: 10.1007/s10067-009-1144-9 · Source: PubMed

5 authors, including:

Paola Ximena Coral-Alvarado
Los Andes University (Colombia)
24 PUBLICATIONS **249** CITATIONS
SEE PROFILE

Natalia Castaño-Rodríguez
UNSW Sydney
48 PUBLICATIONS **1,309** CITATIONS
SEE PROFILE

Adriana Rojas-Villarraga
Fundación Universitaria de Ciencias de la Salud
211 PUBLICATIONS **2,984** CITATIONS
SEE PROFILE

Juan-Manuel Anaya
Universidad del Rosario
729 PUBLICATIONS **12,805** CITATIONS
SEE PROFILE

Clin Rheumatol (2009) 28:757–765
DOI 10.1007/s10067-009-1144-9

ORIGINAL ARTICLE

Systemic sclerosis: A world wide global analysis

Paola Coral-Alvarado · Aryce L. Pardo · Natalia Castaño-Rodriguez · Adriana Rojas-Villarraga · Juan-Manuel Anaya

Received: 17 October 2008 / Revised: 19 January 2009 / Accepted: 19 February 2009 / Published online: 11 March 2009

Abstract The objective of this study was to analyze epidemiological tendencies of systemic sclerosis (SSc) around the world in order to identify possible local variations in the presentation and occurrence of the disease. A systematic review of the literature was performed through electronic databases using the keywords "Systemic Sclerosis" and "Clinical Characteristics." Out of a total of 167 articles, 41 were included in the analysis. Significant differences in the mean age at the time of diagnosis, subsets of SSc, clinical characteristics, and presence of antibodies were found between different regions of the word. Because variations in both additive and nonadditive genetic factors and the environmental variance are specific to the investigated population, ethnicity and geography are important characteristics to be considered in the study of SSc and other autoimmune diseases.

Keywords Clinical characteristics · Epidemiology · Systemic sclerosis

P. Coral-Alvarado · A. L. Pardo · N. Castaño-Rodriguez · A. Rojas-Villarraga · J.-M. Anaya (✉)
Center for Autoimmune Diseases Research (CREA), School of Medicine,
Rosario University, Carrera 24 #, 63-C-69 Bogota, Colombia
e-mail: anayajm@gmail.com

P. Coral-Alvarado · A. L. Pardo · N. Castaño-Rodriguez · A. Rojas-Villarraga · J.-M. Anaya
Corporación para Investigaciones Biológicas, Medellin, Colombia

Background

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown cause characterized by microvasculopathy, fibroblast activation, and excessive production of collagen. SSc is unique in displaying features of three distinct pathophysiologic processes: cellular and humoral autoimmunity, vascular injury, and tissue fibrosis.

SSc is observed predominantly in black females with a peak of incidence between 45 and 64 years of age. The epidemiology of SSc is not definitively established due to the relative rarity of the disease, the difficulty in diagnosis, and the large variability in the clinical manifestations and severity.

This paper shows the epidemiological tendencies in the presentation and occurrence of SSc in different regions of the world.

Materials and methods

Review of literature

Electronic databases (MEDLINE, PUBMED, SCIELO, LILACS, BIREME) were searched up until February 2008 for all studies concerning to the epidemiological tendencies of SSc in humans. The search strategy contained MeSH terms and text words as follows: "Systemic Sclerosis" and "Clinical Characteristics." No other limits were employed. The manuscripts were published in peer-reviewed journals as full papers, not as an abstract or similar, and the literature provided enough information to be considered for comparison. Additionally, reports concerning the disease in childhood were excluded. Studies were included if they met the following requirements: the diagnosis of SSc was accomplished using

the classification criteria for SSc established by the American College of Rheumatology, and the disease was classified as diffuse SSc or limited SSc depending on the extent of skin involvement according to the criteria proposed by LeRoy (http://www.rheumatology.org/publications/classification/systsclr.asp).

Statistical analysis

To perform the meta-analysis, the following information was extracted from each study: (1) author, (2) year of publication, (3) study population, and (4) total cases of local and diffuse SSc (Table 1). Estimation of odds ratio (OR) was possible obtaining the number of individuals with local and diffuse SSc presenting any of the demographic and clinical variables of interest in each study included. Data were analyzed using the Comprehensive Meta-Analysis version 2.0 program (Biostat, Englewood, NJ, USA 2004). The common effect size was calculated using the inverse variance weighting scheme. Both fixed and random effect models were used to calculate summarized OR as well as 95% confidence intervals (CIs) for each variable. The random effect model was chosen because it assumes that true quantities from the individual studies have a probability distribution, and it assigns a more balanced weight to each study. Heterogeneity was calculated by means of the

Table 1 Characteristics of individual studies included in meta-analyses

Ref.	Country	Continent	Sample size	Diffuse	Limited	Meta-analysis[a]
[34]	Europe	Europe	290	117	173	Articular involvement, calcinosis, gender, heart involvement, lung involvement, skin ulcers, telangiectasias
[29]	Italy	Europe	742	177	565	Articular involvement, calcinosis, esophageal involvement, gender, heart involvement, lung involvement, Raynaud phenomenon, skin ulcers, telangiectasias
[23]	UK	Europe	128	78	50	Gender
[33]	Grece	Europe	238	114	124	Articular involvement, esophageal involvement, gender, heart involvement, lung involvement, Raynaud phenomenon, skin ulcers
[31]	Europe	Europe	3,656	1,349	2,101	Articular involvement, esophageal involvement, gender, heart involvement, lung involvement, raynaud phenomenon, skin ulcers
[3]	Brazil	Latin American	32	8	20	Calcinosis, telangiectasias
[11]	Colombia	Latin American	102	85	17	Articular involvement, esophageal involvement, Raynaud phenomenon, telangiectasias
[10]	Colombia	Latin American	19	9	10	Articular involvement, heart involvement
[15][b]	USA	North American	127	24	69	Articular involvement, calcinosis, esophageal involvement, heart involvement, lung involvement, Raynaud phenomenon
[15][c]	USA	North American	247	116	104	Articular involvement, calcinosis, esophageal involvement, heart involvement, lung involvement, Raynaud phenomenon
[13]	Canada	North American	181	29	152	Articular involvement, calcinosis, esophageal involvement, gender, heart involvement, lung involvement, Raynaud phenomenon, skin ulcers, telangiectasias
[40]	Australia	Australia	548	107	307	Gender
Total			6,310	2,213	3,692	

[a] The study that corresponds to the row was included in each of the mentioned analyses

[b] French, subgroup of patients included in Meyer et al. [15] study

[c] North American, subgroup of patients included in Meyer et al. [15] study

Gender male gender, *Esophageal involvement* dysphagia or esophageal dysfunction, *Heart involvement* diastolic dysfunction, abnormal left ventricular eyection fraction or abnormal electrocardiogram, *Lung involvement* interstitial fibrosis or restrictive syndrome, *Skin ulcers* digital ulcers, necrosis, pitting scars or gangrene

Table 2 Comparison among all series of SSc patients

Characteristic	**Europe** Mean[a] 95% CI *N*	**Asia** Mean[a] 95% CI *N*	**North America** Mean[a] 95% CI *N*	**Latin America** Mean[a] 95% CI *N*	
Age at onset (years)	48 (47–48) 5,307	34 (32–36) 128	52 (51–52) 2,151	51 (50–52) 549	
Disease duration (years)	7 (6–7) 4,918	11 (9–13) 128	4 (4–5) 1,039	7 (7–8) 491	
	%. 95% CI *N*	% 95% CI *N*	% 95% CI *N*	% 95% CI *N*	X^2. p[b]
Female	86 (85–87) 7,149	90 (88–90) 560	76 (75–77) 4,590	91 (89–93) 1,168	268,202<0.001
Diffuse SSc	35 (34–36) 7,077	26 (22–26) 385	39 (38–40) 5,199	32 (29–35) 918	45,672<0.001
Limited SSc	61 (59–62) 7,077	33 (28–33) 385	53 (52–55) 5,199	72 (69–74) 1,035	242,191<0.001
Telangiectasias	66 (64–68) 2,093	49 (42–49) 203	63 (61–64) 3,463	67 (63–70) 598	28,380<0.001
Calcinosis	20 (18–21) 1,966	4 (0–4) 75	31 (30–33) 3,710	35 (31–39) 505	118,713<0.001
Raynaud's phenomenon	96 (96–97) 5,364	94 (92–94) 560	94 (94–95) 3,710	94 (92–96) 654	17,062<0.001
Arthralgias or arthritis	30 (27–32) 1,683	58 (54–58) 560	57 (55–58) 3,227	63 (59–67) 509	385,885<0.001
Esophageal involvement	62 (61–64) 5,839	52 (47–52) 560	60 (59–62) 4,096	44 (40–48) 661	99,632<0.001
Pulmonary involvement	42 (40–43) 6,794	60 (56–60) 560	30 (29–32) 4,096	27 (23–30) 751	296,791<0.001
Cardiac involvement	20 (19–21) 6,571	17 (14–17) 460	9 (8–11) 3,004	7 (5–10) 368	183,587<0.001
Renal involvement	8 (8–9) 6,680	9 (7–9) 560	6 (5–7) 3,004	8 (5–10) 371	19,447<0.001
Antinuclear antibody positive	90 (90–91) 4,207	81 (78–81) 560	79 (78–81) 4,319	94 (92–95) 646	243,620<0.001
Anticentromere antibody positive	24 (23–25) 6,658	15 (12–15) 457	24 (23–25) 5,199	64 (60–67) 640	536,888<0.001
Anti-topoisomerase I antibody positive	38 (37–39) 6,912	29 (25–30) 385	17 (16–18) 5,199	21 (18–24) 676	678,952<0.001

95% CI 95% confidence interval

[a] Combined means and confidence intervals for age at onset and disease duration were computed by using only the studies who provided standard deviations of these variables

[b] Chi-squared test with 3 *df*

Table 3 "One study removed" test for statistically significant results of meta-analysis on clinical variables associated with diffuse SSc

Ref.	**Sensitivity analysis (OR [CI])**[a]					
	Calcinosis	**Articular involvement**	**Esophageal involvement**	**Male gender**	**Lung involvement**	**Skin ulcers**
[34]	0.51 [0.29–0.90]	2.83 [1.44–5.54]	NA	2.13 [1.48–3.06]	2.19 [1.50–3.21]	1.49 [1.24–1.80]
[29]	0.51 [0.35–0.74]	2.74 [1.32–5.70]	NS	1.88 [1.37–2.58]	2.01 [1.28–3.17]	1.46 [1.14–1.87]
[23]	NA	NA	NA	2.39 [1.99–2.87]	NA	NA
[33]	NA	2.78 [1.39–5.56]	NS	2.05 [1.44–2.93]	1.85 [1.26–2.70]	1.44 [1.25–1.67]
[31]	NA	1.87 [1.15–3.02]	1.49 [1.12–1.98]	1.95 [1.24–3.08]	2.04 [1.22–3.42]	1.37 [1.02–1.85]
[3]	0.56 [0.36–0.87]	NA	NA	NA	NA	NA
[11]	NA	2.30 [1.18–4.46]	NS	NA	NA	NA
[10]	NA	2.35 [1.20–4.61]	NA	NA	NA	NA
[15][b]	0.61 [0.40–0.94]	2.71 [1.35–5.44]	NS	NA	1.93 [1.32–2.81]	NA
[15][c]	0.65 [0.43–1.00][d]	2.07 [1.05–4.06]	1.40 [1.02–1.93]	NA	2.29 [1.75–2.98]	NA
[13]	0.65 [0.46-0.92]	2.58 [1.26–5.27]	1.40 [1.04–1.89]	2.04 [1.44–2.89]	1.87 [1.31–2.67]	1.50 [1.33–1.70]
[40]	NA	NA	NA	2.15 [1.52–3.06]	NA	NA

NS statistically not significant results, *NA* information not available for this analysis

[a] Results are located in the row that corresponds to the study removed

[b] Results from the French subgroup of patients included in Meyer et al. [15] study

[c] Results from the North American subgroup of patients included in Meyer et al. [15] study

[d] *P* value is borderline

Table 4 Expected power of statistically significant results of meta-analysis on Systemic Sclerosis (SSc)[a]

Expected power										
					Calcinosis				Articular involvement	
Ref.	Population (country)	Patients	Controls per case	Controls	Relative weight		Expected power		Relative weight	
							α=0.05			
							E (calcinosis)=0.29			
					Fixed	Random	Ψ=0.4	Ψ=0.8	Fixed	Random
[13]	Canada	29	5.2	152	3.60	6.36	0.36	0.07	2.44	12.45
[34]	Europe	117	1.5	173	26.44	26.56	0.86	0.13	4.40	13.73
[29]	Italy	177	3.2	565	44.64	33.37	0.99	0.20	9.71	14.76
[3]	Brazil	8	2.5	20	1.34	2.55	0.10	0.05	NA	NA
[15][b]	USA	24	2.9	69	5.74	9.47	0.28	0.06	2.01	11.91
[15][c]	USA	116	0.9	104	18.25	21.69	0.78	0.11	0.81	8.76
[33]	Grece	114	1.1	124	NA	NA	NA	NA	5.33	14.04
[11]	Colombia	85	0.2	17	NA	NA	NA	NA	0.21	3.90
[10]	Colombia	9	1.1	10	NA	NA	NA	NA	0.29	4.85
[31]	Europe	1,349	1.6	2,101	NA	NA	NA	NA	74.82	15.60
[23]	UK	78	0.6	50	NA	NA	NA	NA	NA	NA
[40]	Australia	107	2.9	307	NA	NA	NA	NA	NA	NA
Heterogeneity					*Q*	*df*	*p-value*	I^2	*Q*	*df*
					7.62	5	0.18	34.36	74.09	8

NA information not available for published data, *NS* statistically not significant ($p>0.05$), *Q* Cochran's Test, *df* degree of freedom, I^2 Higgin's Test

[a]The expected probability of exposure in controls is 0.29, 0.43, 0.54, 0.12, 0.36, and 0.38 for calcinosis, articular involvement, esophageal involvement, male gender, lung involvement, and skin ulcers, respectively

[b]French, subgroup of patients included in Meyer et al. [15] study

[c]North American, subgroup of patients included in Meyer et al. [15] study

Cochran's (Q) and Higgins's (I^2) tests. Adjectives of low, moderate, and high were assigned to I^2 values of 25%, 50%, and 75%, respectively. One study removed and stratified analyses by ethnic group (Caucasians and Mestizos) were done to prove sensitivity of results and detect possible causes of heterogeneity between studies. Publication bias was determined using funnel plots and the Egger's regression asymmetry tests.

The expected statistical power to detect true associations between both subsets of SSc and the selected variables were calculated using PS Power and Sample Size Calculations Version 2.1.31 (Copyright© 2004 by William D. Dupont and Walton D. Plummer, Vanderbilt Biostatistics, Nashville, TN, USA). We used the 0.05 level of significance and calculated the expected probability of exposure to the selected variables in individuals with limited SSc across all studies included in the meta-analysis.

A combined proportion was carried out with variables that reported outcomes in frequencies from studies previously mentioned (data not shown). This analysis used sample size and percentages from each study to ponderate results. Additionally, confidence intervals were obtained with a level of significance of 0.05 (Table 2). To investigate the null hypothesis of equal combined proportions in the studies retrieved from four regions (Europe, Asia, North America, and Latin America), the chi-square test was used with 3 *df*. All analyses were performed by means of Microsoft excel and the Statistical Package for the Social Sciences v15 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Review of literature

After an extensive and complete search of the literature, 166 potentially eligible reports were detected. Eight studies were excluded from this number because they were not developed in humans, 47 reports did not specify clinic characteristics of the patients, and 63 were not written in English, French, or Spanish. A total of 41 reports were included for our analyses of which 12 were Latino American series [1–12], ten North American [13–22], 14 European [15, 23–35], four Asian [36–39], and one Australian [40]. In all series, SSc was observed predominantly in women. The mean age at the time of diagnosis was

Expected power							
Articular involvement		Esophageal involvement				Male gender	
Expected power		Relative weight		Expected power		Relative weight	
α=0.05				α=0.05			
E (articular involvement)=0.43				E (esophageal involvement)=0.54			
Ψ=1.3	Ψ=7.2	Fixed	Random	Ψ=1.0	Ψ=1.8	Fixed	Random
0.10	1.00	2.33	8.51	0.05	0.27	2.97	8.22
0.19	1.00	NA	NA	NA	NA	6.77	13.99
0.33	1.00	12.02	21.11	0.05	0.91	13.11	19.05
NA	NA	NA	NA	NA	NA	NA	NA
0.09	0.97	1.56	6.24	0.05	0.21	NA	NA
0.16	1.00	4.36	12.99	0.05	0.56	NA	NA
0.17	1.00	5.85	15.36	0.05	0.59	3.98	10.09
0.08	0.94	1.42	5.77	0.05	0.21	NA	NA
0.06	0.46	NA	NA	NA	NA	NA	NA
0.96	1.00	72.46	30.02	0.05	1.00	64.54	27.52
NA	NA	NA	NA	NA	NA	3.48	9.20
NA	NA	NA	NA	NA	NA	5.15	11.93
p-value	I^2	*Q*	*df*	*p-value*	I^2	*Q*	*df*
0.00	89.20	12.84	6	0.05	53.28	12.73	6.00

46.79 ±13.42 years, and only four series presented lower age at time of diagnosis: Mexico [9] (34 years), Japan [39] (37.8±10.3 years), India [36] (32.75±11.62 years), and Iraq [37] (20 years). Limited SSc was the most frequent cutaneous subset in all series, except for two series in the USA [17, 21], one in the UK [23], three in Brazil [2, 7, 8], and one in Colombia [10], all of which reported the most common subtype as diffuse SSc. Raynaud's phenomenon was the most frequent clinical variable observed in all series. Telangiectasias were reported with a highest frequency in four European series [26–29], one Brazilian series [8] and one USA series [17], while calcinosis was most frequently reported in Brazil [5] and Colombia [11].

The highest rates of esophageal involvement were observed in African–Americans [22], Brazilians [6], and Iraqis [37] in whom a prevalence of this complication was reported in 97%, 87%, and 87%, respectively. Cardiac and kidney involvement were low in most series, only three European [24, 27, 31] and one Brazil [5] reports showed 21–30% and 32%, respectively.

We regrouped data from Europe, Asia, North America, and South America, as shown in Table 2. In all groups, female gender and limited SSc were the predominant association ($p<0.0001$). In Asia, the age at onset was significantly earlier than in other countries ($p<0.0001$), as well as the higher presence of telangiectasias and pulmonary involvement ($p<0.0001$). In Europe, esophageal and cardiac involvement and positive anti-topoisomerase I scoring were the most common findings as compared with other countries ($p=0.0001$). Raynaud's phenomenon was present at the same proportion among all groups.

Within Latin America, the Colombian series showed a later age of onset than the Brazilian series ($p<0.0001$ CI 95% 7.05–10.1). In both Colombia and Brazil, limited SSc was the most frequent subset, although in Brazil, there are more cases of diffuse SSc reported than in Colombia ($p=0.0009$). Gastrointestinal and pulmonary involvements were more frequently reported in Brazilian individuals while the presence of positive anticentromere antibodies was more frequent in the Colombian series ($p<0.0001$).

The type of the antibodies more frequently reported was antinuclear antibodies in most of series. The antibodies anti-topoisomerase I were not exclusive of diffuse SSc since in four series were most common in limited SSc [4, 26, 31, 35].

Meta-analysis

Eleven studies from all the articles retrieved by means of the literature review were used to perform the meta-analysis [3, 10, 11, 13, 15, 23, 29, 31, 33, 34, 40]. Nine clinical characteristics were selected as relevant variables: seven studies were included in the meta-analysis of male gender, five studies in the meta-analysis of telangiectasias, six studies in the meta-analysis of calcinosis, nine studies in the meta-analysis of articular involvement,

Table 4 (continued)

	Expected power									
	Male gender		Lung involvement				Skin ulcers			
Ref.	Expected power		Relative weight		Expected power		Relative weight		Expected power	
	α=0.05				α=0.05				α=0.05	
	E (male gender)=0.12				E (lung involvement)=0.36				E (skin ulcers)=0.38	
	Ψ=1.7	Ψ=2.4	Fixed	Random	Ψ=1.7	Ψ=3.3	Fixed	Random	Ψ=1.2	Ψ=1.5
[13]	0.20	0.45	1.35	7.71	0.26	0.84	1.38	2.26	0.08	0.17
[34]	0.37	0.80	5.35	15.10	0.59	1.00	6.46	9.89	0.12	0.39
[29]	0.62	0.97	10.55	17.98	0.86	1.00	12.87	18.24	0.18	0.65
[3]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
[15][b]	NA	NA	1.78	9.17	0.20	0.70	NA	NA	NA	NA
[15][c]	NA	NA	4.49	14.23	0.49	0.99	NA	NA	NA	NA
[33]	0.31	0.72	4.50	14.24	0.52	1.00	5.31	8.25	0.11	0.34
[11]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
[10]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
[31]	1.00	1.00	71.97	21.58	1.00	1.00	73.99	61.37	0.73	1.00
[23]	0.16	0.39	NA	NA	NA	NA	NA	NA	NA	NA
[40]	0.43	0.85	NA	NA	NA	NA	NA	NA	NA	NA
Heterogeneity	*p-value*	I^2	*Q*	*df*	*p-value*	I^2	*Q*	*df*	*p-value*	I^2
	0.05	52.86	24.08	6.00	0.00	75.08	4.58	4.00	0.33	12.75

seven studies in the meta-analysis of esophageal involvement, seven studies in the meta-analysis of lung involvement, seven studies in the meta-analysis of heart involvement, five studies in the meta-analysis of skin ulcers, and seven in the meta-analysis of Raynaud phenomenon (Table 1).

Association between clinical characteristics and diffuse SSc

Under the random effect model, the analyses showed a negative association between diffuse SSc and calcinosis (OR 0.58, 95% CI 0.39–0.87, p=0.008). On the other hand, individuals with diffuse SSc are more frequently affected by articular involvement (OR 2.48, 95% CI 1.30–4.75, p=0.006), esophageal involvement (OR 1.33, 95% CI 1.01–1.76, p=0.043), lung involvement (OR 2.01, 95% CI 1.42–2.86, p=0.000), and skin ulcers (OR 1.47, 95% CI 1.25–1.71, p=0.000). Additionally, male gender was associated with this presentation of the disease (OR 2.10, 95% CI 1.53–2.87, p=0.000). Under the fixed effect model, heart involvement showed an association with diffuse SSc (OR 12.5, 95% CI 10.46–14.94, p=0.000); nevertheless, this analysis proved to have high heterogeneity (I^2=98.04%). Analyses of telangiectasias and Raynaud phenomenom did not show statistical significance.

Stratified analysis showed that Caucasian individuals with diffuse SSc present less calcinosis (OR 0.41, 95% CI 0.36–0.87, p=0.010). On the other hand, an articular involvement is frequent in both Caucasian and Mestizo patients with diffuse SSc (OR 2.17, 95% CI 1.10–4.30, p=0.028 and OR 10.23, 95% CI 1.60–65.51, p=0.014; respectively). Sensitivity analysis showed significant results for calcinosis, articular involvement, male gender, lung involvement, and skin ulcers (Table 3).

We use the 0.05 level of significance, an OR of exposure in cases relative to controls of 0.4 and 0.8 for calcinosis; 1.3 and 7.2 for articular involvement; 1.0 and 1.8 for esophageal involvement; 1.7 and 2.4 for male gender; 1.7 and 3.3 for lung involvement; and 1.2 and 1.5 for skin ulcers. These ORs represented the 25 and 75 quartiles of the distribution of effect sizes for each clinical variables associated with diffuse SSc. (Table 4).

Study quality

There is no evidence of publication bias according to funnel plots and Egger's regression tests results in the current meta-analyses (for calcinosis, the t value was 1.7, df=4, p=0.17; for articular involvement, the t value was 1.3, df=7, p=0.23; for esophageal involvement, the t value was

1.16, df=5, p=0.3; for lung involvement, the t value was 0.12, df=5, p=0.91; for skin ulcers, the t value was 0.93, df=3, p=0.42; and for gender, the t value was 0.94, df=5, p=0.39).

Discussion

SSc is an autoimmune disease described in patients all over the world, with a variable presentation, lack of precise information, and lack of uniformity in the diagnostic criteria, making it difficult to study its epidemiological features. Nevertheless, significant differences in both clinical and laboratory data were observed among different series from Asia, America, and Europe. Differences between diverse published series might be due to ascertainment bias; however, genetic and environmental factors should be also considered.

A genetic predisposition to SSc is suggested by reports of familial SSc, by animal models, and by disease-association studies, in which a wide variety of genes including those involved in fibrosis, in vascular function and structure, and in autoimmunity has been examined. Several loci had suggested to be in linkage and associated to disease overlap among multiple autoimmune diseases, indicating that SSc might be at the crossroad of autoimmunity. It is well known, however, that the association of genetics variants with complex diseases might vary according to ethnicity and admixture. SSc represents one of the conditions being considered as complex traits when looking for an etiology supported by a genetic basis. The "complex genetic trait" term defines those phenotypes not fitting patterns of Mendelian segregation but showing a preferential familial clustering that cannot be exclusively explained by cultural or environmental effects. Possible causes underlying this departure from Mendelian laws are the presence of genetic heterogeneity, unknown or unmeasurable contributions of low-penetrance common alleles, and environmental factors [41]. There are latter solvents that have been associated with SSc by several rigorous case-control studies that suggest a causal role. Current data about other toxic agents (epoxy resins, vibrations, and welding fumes) do not justify conclusions about their role in SSc [42].

Ethnic and racial differences are considered to influence the occurrence of the disease, and differences in ethnicity may account for diverse subtypes and organ involvement as reported by Mcnearney et al. [22] and Reveille et al. [17]. Other differences in relation with ethnic groups have been reported in other series; for example, most cases of diffuse SSc have been observed in Hispanic and African–Americans [22]. Ethnic differences in HLA associations also have been reported in relation to specific autoantibodies [43].

Several reports suggested that African–American subjects have a more severe disease than Caucasian subjects [4, 14, 17, 20, 22]. These studies confirm the existence of an ethnic variability in the susceptibility to develop SSc and showed significantly more likely to have diffused disease and anti-topoisomerase I antibodies.

Additionally, SSc has been observed in some regions, suggesting a nonrandom distribution of the disease in some population and a possible space-temporal clustering of cases in particular areas. A cluster analysis is of interest in SSc to identify populations with higher prevalences of SSc but remains unknown if these clusters are based on intrinsic factors (genetic) or exposure to an extrinsic variable (environmental) or the interaction of both. Reports have suggested clustering among some populations that may reflect exposure to specific environmental or genetic factors, for example, Silman and colleagues showed a formal epidemiological analysis suggesting a statistically significant cluster of scleroderma in areas to the south and west of London, UK [44]. Valesini et al. [45] identified a geographic cluster of SSc in a small rural area in the province of Rome, Italy. In this analysis, no known environmental factor was identified. Other cluster of SSc was identifying in Choctaw Native Americans in Southeastern Oklahoma, USA without any environmental exposures associated [46].

It has been well documented that SSc has a female preponderance that ranges from 3:1 to 8:1 but until to date, there is no widely accepted biological explanation for the marked female predominance in SSc.

The gender-specific differences of the disease features reflect a modifying influence of sex hormones. Steen and coworkers [47] showed in this study that the overall female to male incidence radio was 3/1 and was slightly higher between 15 and 44 years but slightly lower during the postmenopausal years. This theory of the influence of sex hormones has been suggested in previous studies but rather inconsistent results [48].

The reasons underlying the reported divergences in clinical and laboratory characteristics among patients from different ethnicities are not fully understood, but it is most likely that both genetic and nongenetic factors are responsible for them. A putative role of geographical factors came from data suggesting that the SSc phenotype might differ among subjects from different ethnic backgrounds. The most recent analysis published showed a large local variability of SSc presentations in a European population and preclude the identification of genetic or environmental factors [49]. Because variations in both additive and nonadditive genetic factors and the environmental variance are specific to the investigated population, ethnicity and geography are important characteristics to be considered in the study of SSc and other autoimmune diseases [50, 51].

An accurate description of SSc epidemiology in different geographical regions represents an important approach to unraveling the etiological mechanisms underlying this autoimmune entity.

Disclosures None.

References

1. Christmann de Souza R, Lobato C, Ferreira E et al (2005) Comparison of Reproductive Factors in 117 Limited Scleroderma and 72 Rheumatoid Arthritis Patients. Rev Bras Reumatol 45:114–118
2. Fernandez S, Mittermayer B, Andrade T et al (2005) Interstitial lung disease in patients with progressive systemic sclerosis. A study of 58 cases. J Bras Pneumol 31:300–306
3. Guidolin F, Esmanhotto L, Magro C et al (2005) Prevalence of cutaneous findings in systemic sclerosis patients. Experience of a teaching hospital. An Bras Dermatol 80:481–486
4. Villalba WO, Sampaio-Barros PD, Pereira MC et al (2007) Six-minute walk test for the evaluation of pulmonary disease severity in scleroderma patients. Chest 131:217–222
5. Eloi JC, Franck M, Staub HL et al (1999) Pulmonary fibrosis in progressive systemic sclerosis: frequency and clinical associations. Rev Bras Reumatol 39:75–80
6. Sampaio-Barros PD, Barcelos IK, Oliveira A et al (1999) Gastrointestinal involvement in systemic sclerosis. Rev Bras Reumatol 39:81–86
7. de Azevedo MS, Campos W, Calderaro D et al (2005) High-resolution computed tomography versus chest radiography in the diagnosis of interstitial lung disease in systemic sclerosis. Radiol Bras 38:95–99
8. de Azevedo AB, Sampaio-Barros PD, Torres RM et al (2005) Prevalence of pulmonary hypertension in systemic sclerosis. Clin Exp Rheumatol 23:447–454
9. De Kasep GI, Alarcon-Segovia D (1985) Preliminary epidemiologic data on progressive systemic sclerosis in Mexico. In: Black CM, Myers AR (eds) Systemic sclerosis (Scleroderma). Gower, New York, pp 70–71
10. Mejia R, Vélez P, Avila L et al (2003) Correlación entre los niveles de citoquinas en el lavado broncoalveolar en una cohorte de pacientes del Hospital Militar Central, con esclerosis sistemica (SS), con y sin alveolitis. Rev Colomb Reumatol 10: 256–263
11. Londoño JC, Restrepo JF, Guzman R et al (1998) Estudio descriptivo de 102 pacientes en el Hospital San Juan de Dios de Santa Fe de Bogota. Rev Colomb Reumatol 5:131–142
12. Coral-Alvarado P, Rojas-Villarraga A, Latorre MC et al (2008) Risk factors associated with pulmonary arterial hypertension in colombian patients with systemic sclerosis: review of the literature. J Rheumatol 35:244–250
13. Scussel-Lonzetti L, Joyal F, Raynauld JP et al (2002) Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine (Baltimore) 81:154–167
14. Mayes MD, Lacey JV Jr, Beebe-Dimmer J et al (2003) Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 48:2246–2255
15. Meyer OC, Fertig N, Lucas M et al (2007) Disease subsets, antinuclear antibody profile, and clinical features in 127 French and 247 US adult patients with systemic sclerosis. J Rheumatol 34:104–109
16. Poormoghim H, Lucas M, Fertig N et al (2000) Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum 43:444–451
17. Reveille JD, Fischbach M, McNearney T et al (2001) Systemic sclerosis in 3 US ethnic groups: a comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. Semin Arthritis Rheum 30:332–346
18. Systemic sclerosis: clinical aspects (2001) In: Arthritis and allied conditions 14th ed Philadelphia:1590.
19. Jacobsen S, Ullman S, Shen GQ et al (2001) Influence of clinical features, serum antinuclear antibodies, and lung function on survival of patients with systemic sclerosis. J Rheumatol 28:2454–2459
20. Laing TJ, Gillespie BW, Toth MB et al (1997) Racial Differences in Scleroderma among Women in Michigan. Arthritis Rheum 40:734–742
21. Steen VD, Powell DL, Medsger TA Jr (1988) Clinical correlation and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum 31:196–203
22. McNearney TA, Reveille JD, Fischbach M et al (2007) Pulmonary involvement in systemic sclerosis: Associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 57:318–326
23. Silman A, Jannini S, Symmons D et al (1988) An epidemiological study of scleroderma in the West Midlands. Br J Rheumatol 27:286–290
24. Bryan C, Knight C, Black CM et al (1999) Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum 42:2660–2665
25. Morgan C, Knight C, Lunt M et al (2003) Predictors of end stage lung disease in a cohort of patients with scleroderma. Ann Rheum Dis 62:146–150
26. Nagy Z, Czirjak L (1997) Predictors of survival in 171 patients with systemic sclerosis (scleroderma). Clin Rheumatol 16:454–460
27. Czirják L, Kumánovics G, Varjú C et al (2008) Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis 67:59–63
28. Hesselstrand R, Ekman R, Eskilsson J et al (2005) Screening for pulmonary hypertension in systemic sclerosis: the longitudinal development of tricuspid gradient in 227 consecutive patients, 1992–2001. Rheumatology (Oxford) 44:366–371
29. Ferri C, Valentini G, Cozzi F et al (2002) Systemic sclerosis: demographic, clinical, and serologic features and survival in 1, 012 Italian patients. Medicine (Baltimore) 81:139–153
30. Simeon CP, Armadans L, Fonollosa L et al (1997) Survival prognostic factors and markers of morbidity in Spanish patients with systemic sclerosis. Ann Rheum Dis 56:723–728
31. Walker UA, Tyndall A, Czirjak L et al (2007) Clinical risk assessment of organ manifestations in systemic sclerosis - a report from the EULAR Scleroderma Trials And Research (EUSTAR) group data base. Ann Rheum Dis 66:754–763
32. Alamanos Y, Tsifetaki N, Voulgari PV et al (2005) Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. Semin Arthritis Rheum 34:714–720
33. Vlachoyiannopoulos PG, Dafni UG, Pakas I et al (2000) Systemic scleroderma in Greece: low mortality and strong linkage with HLA-DRB1*1104 allele. Ann Rheum Dis 59:359–367
34. Della Rossa A, Valentini G, Bombardieri S et al (2001) European multicentre study to define disease activity criteria for systemic

sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centers. Ann Rheum Dis 60:585–591
35. Plastiras SC, Karadimitrakis SP, Kampolis C et al (2007) Determinants of Pulmonary Arterial Hypertension in Scleroderma. Semin Arthritis Rheum 36:392–396
36. Sharma VK, Trilokraj T, Khaitan BK et al (2006) Profile of systemic sclerosis in a tertiary care center in North India. Indian J Dermatol Venereol Leprol 72:416–420
37. Al-Adhadh RN, Al-Sayed TA (2001) Clinical features of systemic sclerosis. Saudi Med J 22:333–336
38. Tamaki T, Mori S, Takehara K (1991) Epidemiological study of patients with systemic sclerosis in Tokyo. Arch Dermatol Res 283:366–371
39. Kuwana M, Kaburaki J, Mimori T et al (2000) Longitudinal analysis of autoantibody response to topoisomerase i in systemic sclerosis. Arthritis Rheum 43:1074–1084
40. Roberts-Thomson PJ, Jones M, Hakendorf P et al (2001) Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. Intern Med J 31:220–229
41. Anaya JM, Corena R, Castiblanco J et al (2007) The kaleidoscope of autoimmunity: multiple autoimmune syndromes and familial autoimmunity. Expert Rev Clin Immunol 3:623–635
42. Magnant J, Diot E (2006) Sclérodermie systémique: épidémiologie et facteurs environnementaux. Presse Med 35:1894–1901
43. Kuwana M, Okano Y, Kaburaki J et al (1994) Racial differences in the distribution of systemic sclerosis-related serum antinuclear antibodies. Arthritis Rheum 37:902–906
44. Silman A, Howard Y, Hicklin AJ et al (1990) Geographical clustering of scleroderma in South and West London. Br J Rheumatol 29:92–96
45. Valesini G, Litta A, Bonavita MS (1993) Geographical clustering of scleroderma in a rural area in the province of Rome. Clin Exp Rheumatol 11:41–47
46. Arnett FC, Howard RF, Tan F et al (1996) Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Arthritis Rheum 39:1362–1370
47. Steen VD, Oddis CV, Conte CG (1997) Incidence of systemic sclerosis in Allegheny Country, Pennsylvania. A twenty-year study of hospital diagnosed cases, 1963–1982. Arthritis Rheum 40:441–445
48. Launay D, Hebbar M, Hatron PY (2001) Relationship between parity and clinical and biological features in patients with systemic sclerosis. J Rheumatol 28:509–513
49. Walker UA, Tyndall A, Czirják L et al (2008) Geographic variation of disease manifestations in systemic sclerosis - a report from the EULAR Scleroderma Trials And Research (EUSTAR) group data base. Ann Rheum Dis. [Epub ahead of print]
50. Hudson M, Rojas-Villarraga A, Coral-Alvarado P et al (2008) Polyautoimmunity and familial autoimmunity in systemic sclerosis. J Autoimmun 31:156–159
51. Rojas-Villarraga A, Diaz FJ, Calvo-Páramo E et al (2009) Familial disease, the HLA-DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. J Autoimmun 32:64–69